VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraphs at page 20, line 12 to page 22, line 2 were amended as follows:

In one embodiment the TGF-α polypeptide, related polypeptide, mimetic or functional fragment is a TGF-α polypeptide as set forth in SEQ ID NO:1, SEQ ID NO:3, or a TGFα mimetic selected from the group consisting of formula I, formula II, formula III, formula IV, or formula V, wherein formula I is:

R_1- T - R_2 (I)

wherein R_1 is -NH_2, or R_1 is R_3 - X_3 , wherein R_3 is a polyethylene glycol (PEG) attached to the free NH_2 moiety of X_3 (wherein X_3 is Lys [or Arg] or Asp) and having a molecular weight of PEG of from about 2000 daltons to about 10,000 daltons, or one or more of the following seven amino acids from formula [VI] IV, including either L (natural) or D chiral orientations:

-NH_2-X_{1a} -X_{1a}- Ser - His - Phe - [Gln] Asn - X_3- (SEQ ID NO: 7) (IV)

wherein [X_1] X_{1a} is independently Val, Gly or Ala and X_3 is Lys [or Arg] or Asp;

wherein T is the native sequence of human TGFα (SEQ ID NO. 1) from amino acid residue no. 8 (Cys) to amino acid residue no. [44] 43 (Cys) consisting of native L amino acids; and wherein R_2 is -COOH or one of more of the following seven amino acids, including either L (natural) or D chiral orientations, from formula V:

-X_4- His - X_{1c}- X_4- X_5- X_6- X_{1c}- (SEQ ID NO: 5) (V)

wherein X_4 is Glu or Asp, wherein X_5 is Leu or Ile, wherein X_6 is Asp or Glu, and wherein [X_1] X_{1c} is independently Val, Gly, or Ala.

The invention provides a peptide having TGF-α biological activity, comprising at least an 11-membered peptide compound of formula II [(SEQ ID NO:4)]:

-NH_2- X_{1a}-Cys-His-Ser-X_{1b}-X_2-X_{1a}-X_{1b}-X_{1a}-X_3-Cys COOH (SEQ ID NO:4) (II)

wherein [X_1 is] X_{1a} and X_{1b} are independently Val, Gly, or Ala, wherein X_2 is Tyr or Phe, wherein X_3 is Arg or Lys, and wherein the two Cys moieties form a disulfide bond to create an 11-amino-acid functional peptide having a 10 member loop structure. In addition, at least one or

more of the following amino acids of formula III [(SEQ ID NO:5)] may be added to the C terminus Cys moiety of formula [I] II [(SEQ ID NO:4)]:

$$- X_4 - His - X_{1c} - X_4 - X_5 - X_6 - X_{1c}$$ (SEQ ID NO: 5) (III)

wherein X_4 is Glu or Asp, wherein X_5 is Leu or Ile, wherein X_6 is Asp or Glu and wherein X_{1c} is Val, Gly or Ala. Preferably, X_{1a} is Val, X_{1b} is Gly and X_{1c} is Ala thereby producing an 11, 12, 13, 14, 15, 16, 17 or 18 amino acid peptide. Preferably, X_2 is Tyr, and X_3 is Arg. Accordingly, in one embodiment the functional peptide of the invention has a sequence:

NH_2-X_{1a}-Cys-His-Ser-X_{1b}-X_2-X_{1a}-X_{1b}-X_{1a}-X_3–Cys-X_4-His-X_{1c}-X_4-X_5-X_6-X_{1c}–COOH (SEQ ID NO:6)

SEQ ID NO: 6 forms a 10 member loop structure with a 7 member tail that can be varied in length. In addition, SEQ ID NO: 6 can form dimmers comprising, for example, a 34-mer peptide. Accordingly, the functional peptide can be from about 10 to 18 amino acids in length (*e.g.* 10, 11, 12, 13, 14, 15, 16, 17, or 18 amino acids) wherein X_{1a} is Val, X_{1b} is Gly, X_{1c} is Ala and X_4 is [Gly] Glu and may also comprise hetero- or homo-dimers of various TGF-α peptides described herein. Such dimmers may have greater or reduced activities as compared to monomers.

The invention further provides an active TGF-α57 polypeptide (SEQ ID NO:3), wherein TGF-α57 is a 57 amino acid polypeptide having the formula VI:

Ser - Leu – Ser – Leu – Pro – Ala – Met – Human TGFα (SEQ ID NO: 3) (VI)

Wherein human TGFα is a 50 amino acid polypeptide having a sequence as set forth in SEQ ID NO:1.

The paragraphs at page 52, lines 1-27 were amended as follows:

The invention further provides a bifunctional compound that acts as a TGFα mimetic, comprising a compound of formula III:

Loop peptide N-terminus-linker-cyclic $C_4H_8N_2$- linker- Loop peptide N-terminus (VII)

Wherein the linker moiety is designed to link the N-terminus of the Loop peptide to a nitrogen atom of the ring $C_4H_8N_2$ and wherein the "loop peptide" comprises at least an 11-membered peptide compound of formula II:

NH_2- X_{1a}-Cys-His-Ser-X_{1b}-X_2-X_{1a}-X_{1b}-X_{1a}-X_3-Cys COOH (SEQ ID NO:4) (II)

wherein $X_{1a,}$ and X_{1b} are independently Val, Gly, or Ala; X_2 is Tyr or Phe; X_3 is Arg or Lys; and the two Cys moieties are linked via a disulfide bond to form an at least 11-amino acid functional peptide having TGF-α activity. Preferably, at least one or more of the following amino acids are added to the C terminus Cys moiety from formula III, below:

- X_4 - His - X_{1c} - X_4 - X_5 - X_6 - X_{1c} (SEQ ID NO: 5) (III)

wherein X_4 is Glu or Asp, wherein X_5 is Leu or Ile, [and] wherein X_6 is Asp or Glu and wherein X_{1c} is Val, Gly or Ala. Preferably, X_{1a} is Val, X_{1b} is Gly and X_{1c} is Ala. Preferably the linker group is independently selected from the group consisting of substituted or unsubstituted C_{1-6} alkoxy, xylenyl, wherein the substitutions are selected from the group consisting of: oxo, epoxyl, hydroxyl, chloryl, bromyl, fluoryl, and amino. Preferably, X_2 is Tyr, and X_3 is Arg. Most preferably, the functional peptide is 18 amino acids in length wherein X_{1a} is Val, X_{1b} is Gly, X_{1c} is Ala and X_4 is [Gly] Glu.